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Unifying Research and Reimbursement Decisions: Case Studies Demonstrating the Sequence of Assessment and Judgments Required

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ABSTRACT

Background: The key principles regarding what assessments lead to different types of guidance about the use of health technologies (Only in Research, Approval with Research, Approve, or Reject) provide an explicit and transparent framework for technology appraisal. **Objective:** We aim to demonstrate how these principles and assessments can be applied in practice through the use of a seven-point checklist of assessment. **Methods:** The value of access to a technology and the value of additional evidence are explored through the application of the checklist to the case studies of enhanced external counterpulsation for chronic stable angina and clopidogrel for the management of patients with non–ST-segment elevation acute coronary syndromes. **Results:** The case studies demonstrate the importance of considering 1) the expected cost-effectiveness and population net health effects; 2) the need for evidence and whether the type of research required can be conducted once a technology is approved for widespread use; 3) whether there are sources of uncertainty that cannot be resolved by research but only over time; and 4) whether there are significant (opportunity) costs that once committed by approval cannot be recovered. **Conclusions:** The checklist demonstrates that cost-effectiveness is a necessary but not sufficient condition for approval. Only in Research may be appropriate when a technology is expected to be cost-effective due to significant irrecoverable costs. It is only approval that can be ruled out if a technology is not expected to be cost-effective. Lack of cost-effectiveness is not a necessary or sufficient condition for rejection.

Keywords: cost-effectiveness, coverage with evidence development, health technology assessment, only in research, reimbursement decisions, research decisions.

Introduction

In an effort to stem the rising health care costs, many health systems now require that a new technology demonstrate value (i.e., that the expected additional health benefits of the technology justify its additional costs). In publicly funded health systems such as the UK National Health Service (NHS), this is achieved by comparing the additional health gained from the new technology to the health expected to be forgone elsewhere in the system (opportunity cost, which is often assessed through the use of a cost-effectiveness threshold); that is, the technology is considered cost-effective if it offers positive net health benefits.

Even in health systems in which there is an absence of firm budget constraints or those that do not explicitly consider cost, there is often a focus on the magnitude of health benefits of the technology, which are informally weighed against costs. In this case, the existence of opportunity cost remains but it may manifest in terms of nonhealth expenditure. Therefore, decisions about health care technologies should consider including an assessment of the value of access to the technology, typically relying on evidence about clinical effectiveness, impact of the technology on long-term health and potential harms, costs, and some assessment of the opportunity cost of health that is likely to be forgone if the technology is approved for use.

These evidential requirements present a challenge to such decisions because often decisions are made earlier, shortly after regulatory approval, when the evidence base is least mature. Consequently, the assessment of value is uncertain and subsequent decisions about the use of the technology are likely to be uncertain. For example, approval of the technology may result in resources being wasted if the expected positive net health effects are not realized in practice, whereas rejecting the

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Table 1 – Checklist for coverage with evidence development decisions.

Point	Assessment	Judgment (based on estimates of expected net health benefit)	
	Types of analyses required	Yes	No
1	**Is the technology cost-effective?** • Estimate of expected cost-effectiveness at population level		
2	**Are there significant irrecoverable costs?** • Estimate of capital investment costs, upfront costs of treatment, learning and training costs, other potential irrecoverable costs • Assessment of whether decisions are irreversible • Assessment of whether costs are sufficiently significant to influence guidance		
3	**Does more research seem worthwhile?** • Probability that technology is cost-effective • Estimate of expected consequences of uncertainty		
4*	**Is the research possible with approval?** • What type of evidence is required? • Can the research be conducted if the technology is approved for use?		
5	**Will other sources of uncertainty resolve over time?** • Estimate of changes in the price of technology and comparators, new technology entering, other evidence underway, other potential sources		
6	**Are the benefits of research greater than the costs?** • Estimate of the likelihood that the research will be conducted, how much uncertainty will be resolved, when the results will become available, and the impact of other sources of uncertainty • Estimate of the expected costs of research		
7	**Are the benefits of approval greater than the costs?** • Comparison of the benefits of approval and the opportunity costs (e.g., value of research forgone as a consequence of early access)		

* For technologies not expected to be cost-effective at point 1, point 4 becomes "Is the research possible without approval?"

technology may risk failing to provide access to a valuable intervention if the net health effects prove to be greater than expected. Therefore, the need for and value of additional evidence is an important consideration when making decisions about the use of technologies [1–3]. This is even more critical when approval of a technology for widespread use might reduce the prospects of conducting the type of research that would provide the evidence needed [4]. In these circumstances, there is a trade-off between the net health effects to current patients from early access to the technology and the net health effects to future patients from withholding approval until valuable research has been conducted [5]. In making these trade-offs, consideration should also be given to uncertain events in the near or distant future, which may change the value of the technology and the need for evidence [6].

Generating additional evidence through research also consumes valuable resources that could be devoted to improving health outcomes elsewhere. Importantly, implementing approval of a new technology may commit resources that cannot subsequently be recovered if guidance changes at a later date [7–9]. Therefore, guidance about a technology will depend on whether the benefits of research are likely to exceed the costs of research and whether the benefits of early approval of the technology are expected to be greater than the loss resulting from withholding approval until valuable research is conducted or other sources of uncertainty are resolved. Until recently, decisions in many health care systems have been largely binary (i.e., approval or rejection of the technology). However, new decision options that allow patients early access to promising new technologies while limiting the risks associated with making wrong treatment choices until more evidence is established have emerged. Examples include conditional coverage options such as "Only in Research" (OIR) and "Approval with Research" (AWR) decisions: The former restricts the use of new technology to only those patients who are involved in research, whereas the latter approves the technology for widespread use on the condition that additional evidence to support its continued or expanded use be collected.

A review of different health care systems' policies for coverage decisions linked to evidence development has been presented elsewhere [10]; this review identified a lack of clear guidance on the specific circumstances under which an OIR or AWR scheme may be an appropriate policy option. Therefore, Claxton et al [10] set out to establish the key principles of what assessments are needed to inform OIR and AWR recommendations. The assessments identified fall into four broad areas: 1) expected cost-effectiveness and population net health effects; 2) the need for evidence and whether the type of research required can be conducted if a technology is approved for widespread use; 3) whether there are sources of uncertainty that cannot be resolved by research but only over time; and 4) whether there are significant (opportunity) costs that, once committed by approval, cannot be recovered if guidance were to change at a later date. A conceptual framework and algorithm has been developed that identifies the sequence of assessment and decisions leading to a particular type of guidance (OIR, AWR, Approve, or Reject) regarding the use of health technologies [10].

The sequence of assessment from this algorithm can be summarized using a seven-point checklist (Table 1). A judgment at each point of the checklist (based on estimates of expected net health benefits at each point) leads to a particular type of guidance (see Appendix Table S1 in Supplemental Materials found at: 10.1016/j.jval.2015.05.003 for the complete list of possible pathways). All seven assessments do not necessarily need to be undertaken because sometimes earlier decisions will lead directly to guidance.

The purpose of this article is to demonstrate how these principles and assessments can be applied in practice to inform

policy choices of OIR, AWR, Approve, or Reject. Two case studies that explore situations in which OIR or AWR might be particularly relevant and challenging have been selected for this purpose. We describe each checklist point of assessment and examine how each of the assessments might be informed on the basis of the type of evidence and analysis currently available and what additional information and/or analyses might be required.

Case Studies

The two case studies selected are 1) enhanced external counterpulsation for chronic stable angina (EECP), and 2) clopidogrel for the management of patients with non–ST-segment elevation acute coronary syndromes (CLOP). The cost-effectiveness of EECP and clopidogrel has been examined previously as part of the National Institute for Health Research Health Technology Assessment program and the National Institute for Health and Care Excellence (NICE) Multiple Technology Appraisal, respectively [11–13]. The existing methods of appraisal have been taken as the accepted starting point. A range of additional information was sought and further analysis conducted to inform the sequence of assessment and judgments required when completing the OIR/AWR checklist.

EECP is a noninvasive procedure used to provide symptomatic relief from stable angina. The analysis compares EECP (adjunct to standard therapy) with standard therapy alone. Randomized controlled trial (RCT) evidence suggests an improvement in health-related quality of life with EECP at 12 months. To characterize the uncertainty associated with possible longer durations of treatment effect, formal elicitation of expert clinical judgment was undertaken. This provided an estimate of the probability, with uncertainty, of a patient continuing to respond to treatment with EECP in subsequent years [12].

EECP is expected to be cost-effective but with potentially significant irrecoverable costs. These irrecoverable costs include both 1) capital costs of equipment and 2) large initial per-patient treatment costs, combined with a chronic condition in which a decision not to treat a particular patient can be changed at a later date when the results of research become available or other events occur. Consequently, these irrecoverable costs might influence the type of guidance; for example, OIR rather than Approve [9].

CLOP (used for up to 12 months) in combination with low-dose aspirin was recommended by NICE after a multiple technology appraisal for patients with non–ST-segment-elevation acute coronary syndrome who presented with a moderate to high risk of ischemic events (TA80 in 2004 and updated in 2010 in CG94) [14,15]. AWR was considered during the appraisal of CLOP. Four alternative treatment durations of CLOP of 12, 6, 3, and 1 month were compared with standard therapy (with low-dose aspirin). CLOP is expected to be cost-effective with no significant irrecoverable costs and illustrates a number of important characteristics, including 1) the impact of other sources of uncertainty (price change following patent expiry) on the value of research, and 2) interpretation of multiple alternatives.

Assessments Required

Point 1—Is the Technology Expected to Be Cost-Effective?

The sequence of assessment starts with cost-effectiveness and expected impact on population net health effect (NHE) [16,17]. This requires information about prevalence and future incidence of the population and a judgment about the time horizon over which the technology will be used [6]. The scale of the population NHE and how it accumulates over time are important for subsequent assessments; for example, the NHE for current patients must be compared with the benefits to future patients and the significance of irrecoverable opportunity costs of initially negative NHE must be determined.

There is a large prevalent population (109,800) eligible for EECP relative to future incident cohorts (9500 per annum) in chronic stable angina [18]. For CLOP, given the acute nature of non–ST-segment-elevation acute coronary syndrome, only incident populations are eligible for treatment (60,000 per annum) [13]. The total population NHE for EECP and CLOP, assuming the technologies will be used to treat the population over 10 years, is reported in Table 2. EECP is just expected to be cost-effective at a threshold of £20,000 per quality-adjusted life-year (QALY) gained. The incremental NHE is 1405 QALYs. For CLOP, there are four treatment durations of 12, 6, 3, and 1 month as well as current NHS treatment (aspirin alone). The results indicate that 12-month treatment is expected to be cost-effective at a threshold of £20,000 per QALY, with a difference in NHE of 495 QALYs between 12 and 6 months.

The "investment profile" of how NHE accumulates over time for EECP is illustrated in Figure 1. The initial costs of treatment are high and far in excess of the immediate health benefits in the initial period of treatment. The negative NHE is gradually offset by the positive NHE at the "breakeven" point of 17 years (14 years at a patient level). Only after 24 years is the incremental NHE reported in Table 2 achieved. A similar effect is observed in CLOP: The breakeven points for CLOP are 11 years (5 years at patient level) for 12-month treatment against standard NHS care, 27 years (21 years at patient level) for 12- month treatment against 6-month treatment, and 4 years (rather than 2 years) for 1 month-treatment against NHS care.

In summary, both EECP and CLOP are expected to be cost-effective. From the complete list of 35 possible pathways that lead to a particular type of guidance (see Appendix Table S1 in Supplemental Materials), a "yes" at point 1 leaves 23 potential pathways to be assessed at the next point on the checklist.

Point 2—Are There Significant Irrecoverable Costs?

The second point on the checklist requires an assessment of whether there are irrecoverable costs and a judgment of their *potential* significance. Irrecoverable costs are those that, once committed, cannot be recovered if guidance is changed at a later date. They are most commonly thought of as the capital costs of new equipment or facilities with a long life expectancy. These costs are usually annuitized and allocated pro rata to the number of patients likely to be treated during the lifetime of the equipment. Treating these upfront costs as if they are paid per patient will have no effect as long as guidance remains unchanged. The possibility that initial approval might be withdrawn before the end of the lifetime of the equipment (e.g., research reports become available or other sources of uncertainty resolve) requires account to be taken of the fact that, although future patients will no longer receive the technology, the total cost of the equipment remains unchanged (i.e., must be allocated to the smaller number of treated patients).

Irrecoverable (opportunity) costs are also present when the initial negative per-patient costs of treatment are only compensated by later health benefits. The presence of this type of irrecoverable opportunity cost, which offers an investment profile of initially negative NHE (Fig. 1), is very common. Its potential significance, however, depends on whether there is sufficient flexibility in when a patient's treatment can be initiated. For example, if the treatment of a presenting patient can be delayed until uncertainty is resolved, then the commitment of these irrecoverable opportunity costs can be avoided (i.e., they are

Table 2 – Expected cost-effectiveness of EECP and CLOP for the population.

				Cost-effectiveness threshold			
				£20,000 per QALY		£30,000 per QALY	
Treatment (EECP)	Costs (£ million)	QALY	ICER (£/QALY)	NHE QALY (£ million)	Incremental NHE, QALY (£ million)	NHE QALY (£ million)	Incremental NHE, QALY (£ million)
EECP	896	1,435,787	19,391	1,391,001 (27,820)	1405 (28)	1,405,930 (42,177)	16,334 (490)
Standard*	–	1,389,596	–	1,389,596 (27,792)		1,389,596 (41,688)	
Treatment (CLOP)	**Costs (£ million)**	**QALY**	**ICER (£/QALY)**	**NHE QALY (£ million)**	**Incremental NHE, QALY (£ million)**	**NHE QALY (£ million)**	**Incremental NHE, QALY (£ million)**
CLOP12†	10,395	4,194,554	18,663	3,674,813 (73,496)	495 (9.9)	3,848,060 (115,442)	2,798 (83.9)
CLOP6†	10,257	4,187,151	10,477	3,674,318 (73,486)	3,465 (69.3)	3,845,262 (115,358)	4,736 (142)
CLOP3†	10,180	4,179,874	9,396	3,670,853 (73,417)	3,324 (66.5)	3,840,526 (115,216)	4,305 (129)
CLOP1†	10,122	4,173,605	4,961	3,667,529 (73,351)	7,502 (150)	3,836,221 (115,087)	8,327 (250)
NHS‡	10,072	4,163,629	–	3,660,027 (73,201)	–	3,827,894 (114,837)	–

CLOP, clopidogrel for the management of patients with non–ST-segment elevation acute coronary syndromes; EECP, enhanced external counterpulsation for chronic stable angina; ICER, incremental cost-effectiveness ratio; NHE, net health effect; NHS, National Health Service; QALY, quality-adjusted life-year.

* Only the additional costs and effects of EECP over and above standard therapy are considered in the analysis.

† CLOP12, CLOP6, CLOP3, and CLOP1 correspond to treatment with clopidogrel as an adjunct to standard therapy for 12, 6, 3, and 1 month, respectively.

‡ Lifetime treatment with standard therapy alone (including aspirin).

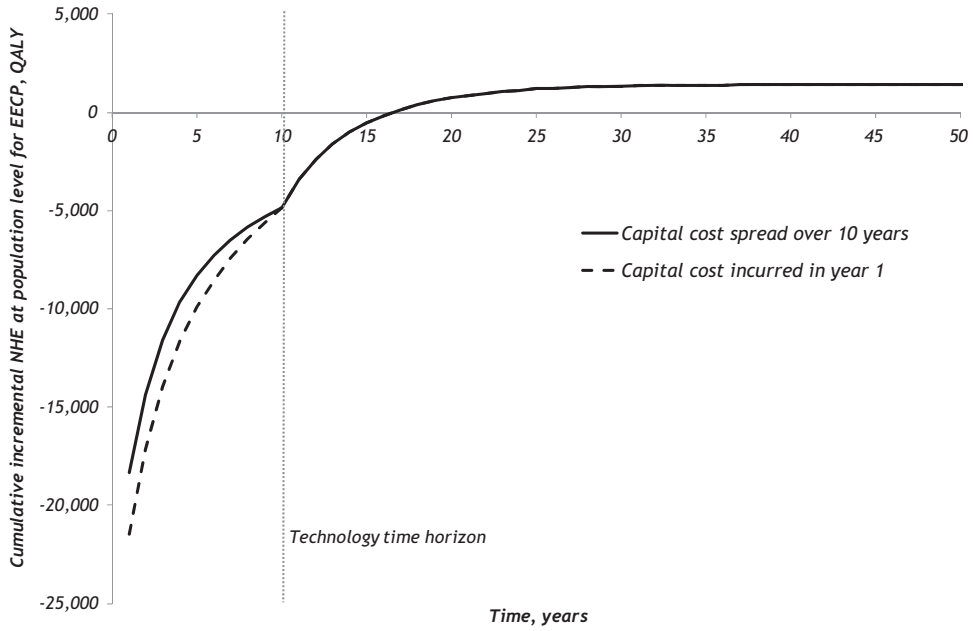

Fig. 1 – Cumulative incremental NHE of EECP for the population. The initial costs of EECP treatment are high and far in excess of the immediate health benefits. These negative NHEs are offset by the positive NHE after 17 years. The NHE is also affected by the timing of expenditure; for example, whether expenditure is treated like a consumable cost by spreading the capital cost of equipment over the technology time horizon of 10 years or whether it is incurred in full in the first year of purchase. EECP, enhanced external counterpulsation for chronic stable angina; NHE, net health effect; QALY, quality-adjusted life-year.

potentially significant). If the decision to treat cannot be delayed, however, these type of irrecoverable costs cannot be avoided; thus, they will have no influence on the type of guidance (i.e., irrecoverable costs are present but are not potentially significant).

Whether the presence of potentially significant irrecoverable costs is likely to influence the type of guidance depends on whether guidance is likely to change in the near or distant future. This in turn depends on whether research is likely to be undertaken and when it is likely to be reported, as well as other events that might occur. These factors are assessed at points 5 and 6 in the checklist. Therefore, whether the presence of irrecoverable costs changes the type of guidance will become clear only at the final point 7 in the checklist. The presence and *potential* significance of any irrecoverable costs, however, can be assessed at this point.

For EECP, the irrecoverable capital cost represents 19% of the total cost. This will have no influence on the expected cost-effectiveness if guidance does not change during the lifetime of the equipment. Figure 1 shows the effect on population NHE when these capital costs are incurred in full in the first year rather than allocated per patient over the lifetime of the equipment. The cumulative incremental NHE is more negative in the first 10 years, but the "investment profile" for EECP is no more risky. Even in the absence of capital costs, EECP exhibits irrecoverable opportunity costs, with initially negative NHE per patient treated. EECP is also for a chronic and stable condition in which there is considerable flexibility in when a particular patient might start treatment with EECP. As a consequence, the treatment of presenting patients could be delayed until the results of research become available, thus avoiding the commitment of irrecoverable opportunity costs. Therefore, the investment profile for EECP has potentially significant irrecoverable costs that could influence the type of guidance.

CLOP also exhibits irrecoverable opportunity costs, with initially negative NHE per patient treated. CLOP, however, is a treatment for acute coronary syndromes in which there is insufficient flexibility to delay the initiation of treatment for presenting patients until the results of research reports become available or other sources of uncertainty resolve. Therefore, in contrast to EECP, the irrecoverable opportunity costs exhibited by CLOP should not be judged to be potentially significant because they cannot be avoided by delaying the initiation of treatment for particular patients. As a consequence, they do not have the potential to influence guidance.

In summary, EECP has significant irrecoverable costs, but CLOP is not expected to have significant irrecoverable costs that would influence guidance. A "yes" at point 2 for EECP and a "no" at point 2 for CLOP reduce the potential pathways from 23 to 17 (for EECP, assessments 13–29 in Table S1) and 6 (for CLOP, assessments 1–6 in Table S1), respectively, to be assessed at the next point on the checklist.

Point 3—Does More Research Seem Worthwhile?

The third point on the checklist requires an assessment of the potential benefits of conducting further research. This requires judgments about 1) how uncertain a decision to approve or reject a technology might be based on expected cost-effectiveness, and 2) whether the scale of the likely consequences of this uncertainty might justify further research. If the potential benefits of further research are unlikely to justify the costs, then a judgment that more research does not seem worthwhile will lead directly to guidance (Approve or Reject if the technology is or is not expected to be cost-effective, respectively).

EECP is expected to be cost-effective, but estimates of cost and QALYs are uncertain; thus, there is a chance that a decision to approve EECP will be incorrect. Some assessment of the likely consequences of approving EECP when standard care might be better can be informed by probabilistic sensitivity analysis (PSA), which provides the joint estimate of uncertainty over the model inputs [17]. The distribution of consequences (i.e., the frequency of errors in the decision to approve EECP across the PSA

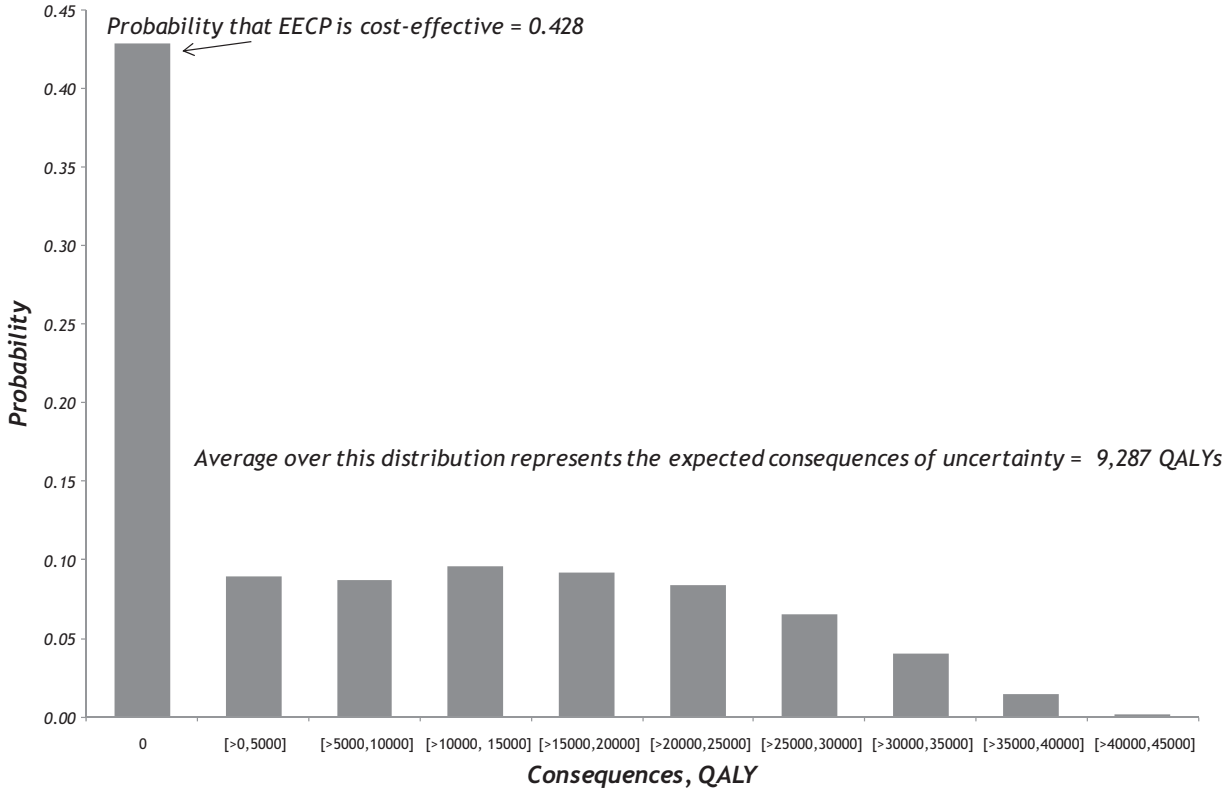

Fig. 2 – Distribution of the consequences of uncertainty for EECP. Most commonly, there are no consequences because a decision to approve EECP is correct 42.8% of the time (i.e., frequency of error in the probabilistic sensitivity analysis simulations). However, when EECP offers a lower NHE than standard care, the consequence of error may be relatively small, for example, 9% are less than 5000 QALYs. However, there is a small chance of 5.7% that they are greater than 30,000 QALYs. The average over this distribution provides the expected consequences of uncertainty of 9287 QALYs. EECP, enhanced external counterpulsation for chronic stable angina; QALY, quality-adjusted life-year.

simulations) is illustrated in Figure 2. Most commonly, there are no consequences because EECP is the correct decision in 42.8% of the simulations. When EECP offers a lower NHE than standard care, the consequence of error may be relatively small; for example, 9% are less than 5000 QALYs. There may, however, be very large consequences, albeit only with a chance of 5.7% that the consequences are greater than 30,000 QALYs. The average over this distribution provides the expected consequences of uncertainty of 9287 QALYs. These expected consequences can be interpreted as an estimate of the population NHE that could be gained over the technology time horizon if the uncertainty could be resolved immediately; that is, it indicates an expected upper bound on the benefits of more research, which is the expected value of perfect information [9,19,20].

CLOP with 12-month duration is expected to be not only cost-effective but also uncertain. Decisions involving multiple alternatives require a judgment of the level of uncertainty, how this uncertainty is distributed across the various alternatives, and what the consequences are likely to be. In this case, there is a 52% chance of no consequences because the 12-month duration with CLOP is the correct decision. When it is not correct, there is a greater chance of relatively small consequences (30% are <10,000 QALYs), which occur predominantly when the 6-month duration offers the highest NHE. There is a small chance of larger consequences (<5% that they are >30,000 QALYs) when standard NHS treatment offers the highest NHE; that is, there remains important uncertainty about the cost-effectiveness of CLOP itself, not only its duration. The expected consequence of uncertainty is 5194 QALYs.

The uncertainty described above reflects uncertainty within the set of assumptions used to estimate expected costs and QALYs. When more than one scenario (alternative view about assumptions) may be credible, there will be uncertainty *between* as well as *within* scenarios. The "weighting" of scenarios can be made explicit by assigning probabilities to represent how credible each is believed to be. For EECP, alternative scenarios might be 1) no QALY benefits beyond 12 months (scenario A); 2) benefits sustained for a lifetime (scenario B); and 3) sustained for 4 years (scenario C). Formal elicitation of the judgment of clinical experts about the likelihood of QALY gains in subsequent years was undertaken [12], resulting in probabilities of 0.243, 0.353, and 0.404 for scenarios A, B, and C, respectively. Applying these weights to the simulated output from the PSA gives an estimate of expected consequences of uncertainty of 13,081 QALYs.

In summary, additional research is required for both EECP and CLOP because the probability that EECP and CLOP is the correct decision is around 50% and there are major expected consequences in terms of NHE if an incorrect decision is made. A "yes" at point 3 for both EECP and CLOP reduces the potential pathways to be assessed at the next point on the checklist from 17 to 14 for EECP (i.e., assessments 13–26 in Table S1) and from 6 to 5 for CLOP (i.e., assessments 1–5 in Table S1).

Point 4—Is Research Possible with Approval?

The fourth point on the checklist requires an assessment of what type of evidence is needed and a judgment of whether research can be conducted while the technology is approved. The

judgment at this point determines whether AWR or OIR is a possibility. This depends, in part, on whether the type of evidence that is needed requires an experimental research design; for example, more precise estimates of relative treatment effect are likely to require an RCT to avoid selection bias, but this is unlikely to be possible once a technology is approved for widespread use. Therefore, the fourth point requires judgments about 1) how important particular types of parameters are to estimates of cost and QALY; 2) what values these parameters would have to take to change a decision; 3) how likely it is that parameters might take such values; and 4) what the consequences would be if they did—that is, what might be gained in the NHE if the uncertainty could be immediately resolved?

A summary of the direction and strength of the relationship between model inputs (the parameters) and outputs (costs and QALYs) can be provided by calculating elasticities (i.e., the proportionate change in the NHE of each alternative due to a 1% change in the value of the parameter). These do not, however, directly help the assessment of what values parameters must take to change decisions and how likely such values might be. PSA can be used to decompose the overall probabilities into the contribution that each parameter (or group of parameters) makes: the expected value of perfect parameter information (EVPPI). For CLOP, uncertainty in the estimate of the relative treatment effect on the risk of death contributes most to the probability of error associated with 12 months of treatment because this is the only parameter that (alone) might take values that could make any of the other alternatives cost-effective.

An assessment of the likely consequences of this uncertainty is now required. Again, the results of PSA can inform this judgment because estimates of the expected consequences of uncertainty associated with each parameter (or group of parameters) combines both uncertainty in its potential values and their importance in terms of changing decisions. The corresponding estimate of the consequences of uncertainty (or gains by resolving this uncertainty through additional research) for the relative treatment effect of the 12-month duration of CLOP is 4433 QALYs. Because more precise estimates of relative effect are likely to require an RCT, a judgment that the type of research needed will not be possible if CLOP is approved may be reasonable. The potential benefits, however, of resolving the uncertainty associated with other groups of parameters (e.g., costs [547 QALYs] and natural history parameters [369 QALYs]) might mean that other types of cheaper, nonexperimental research could be worthwhile as well.

In situations in which more than one scenario might be regarded as credible, there will be uncertainty *between* as well as *within* each of the scenarios. The same analysis can be used to identify the expected consequences of uncertainty associated with the alternative scenarios themselves; that is, what might be gained if evidence could immediately distinguish which scenario was "true." For EECP, using the "elicited weights" for each scenario, the overall expected consequences of uncertainty (combining the consequences within and between scenarios) are 14,146 QALYs. In this case, the expected consequences of uncertainty between the scenarios (13,202 QALYs) are much greater than what might be potentially gained from resolving the uncertainty within each scenario (1765 QALYs). Therefore, unlike CLOP, most of what might be gained from further evidence about EECP (in the absence of formal elicitation) would be evidence that could help distinguish between the scenarios rather than the parameters associated with each.

In summary, more research appears to be worthwhile for EECP, but whether the research required to generate the evidence needed can be conducted while the technology is approved for widespread use is not clear. Therefore, a "yes/no" conclusion is reached at point 4 for EECP. For CLOP, more research appears to be worthwhile in the form of an RCT to reduce uncertainty in the estimate of relative treatment effect on the risk of death. Because it is unlikely that the research could be conducted while CLOP is approved for use—it may be unethical to enroll patients into the trial if the treatment is already approved for widespread use—a "no" conclusion is reached at point 4 for CLOP. This reduces the potential pathways from 5 to 3 for CLOP (assessments 3–5 in Table S1), whereas the number of potential pathways for EECP remains unchanged for the next point of assessment on the checklist.

Point 5—Will Other Sources of Uncertainty Resolve Over Time?

The fifth point on the checklist requires an assessment of whether changes are likely to occur in the future that will influence the cost-effectiveness of the alternative technologies and the potential benefits of research. This requires information about 1) changes in the price of the technology and its comparators, 2) the emergence of new technologies that might make existing ones obsolete or change their cost-effectiveness, and 3) other relevant research reporting.

Changes in price influence not only the expected cost-effectiveness but also uncertainty and the potential benefits of research to future patients; for example, if the price falls significantly just before the results of research become available, the potential benefits will not be realized because approval of the technology will be less uncertain. A change in the price of a technology (or comparators) will affect the value of research because a shift in the distribution of NHE from a technology relative to its comparators will alter the distribution of incremental NHE. For a technology that is expected to be cost-effective, a price reduction will generally reduce the value of additional research because the probability of decision error and the consequences of error tend to fall. This will ultimately affect final guidance. For example, AWR might be revised to Approve if the benefits of early approval now exceed the value of additional evidence. Information about major changes in price and the likely extent of the change are required. The entry of a new technology may also make existing technology obsolete; even when it does not, it tends to change the relative cost-effectiveness of the alternatives, thereby influencing how uncertain a decision to approve the original technology will be for future patients. Research that is already underway, commissioned, or likely to be undertaken is also relevant because it might have an impact on recruitment rates, and there is a chance that it will change the estimate of cost-effectiveness when results are reported.

For the case studies, a number of potential sources of information were examined to identify clinical research underway at the time of appraisal, including national and international trial registries and other databases that report NHS-funded research [16]. Despite an assiduous search, no records relevant to the case studies were identified. This may suggest that no other research was ongoing, or it may indicate that currently available sources are incomplete and/or difficult to access. The patent for CLOP was expected to expire 7 years later. Therefore, the estimate, reported by the Office of Fair Trading, that on average generic prices tend to be 25% of the original drug price was used in the subsequent analysis. A number of potential sources of information were examined to identify the entry of new technologies, including sources related to NICE topic selection; information about license applications; clinical research in phase I, II, and III; and evidence of the probability that earlier phase research leads to entry and the likely time of entry. The information that was available indicated that one new technology relevant to CLOP might have been expected to enter the market.

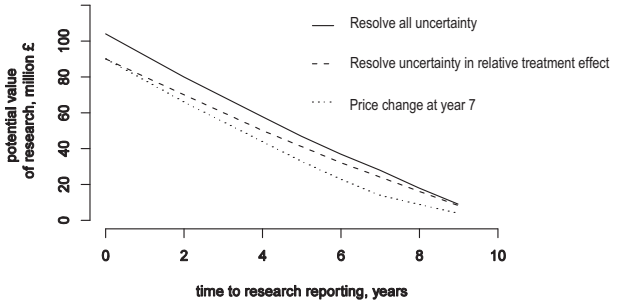

Fig. 3 – Potential value of research and time to report (CLOP). The potential value of research declines with the time it takes research to report, which gives an indication of the value of improving the timeliness of research. Research will not resolve all uncertainty, and other sources of uncertainty, such as price change, will have an impact on the value of research. CLOP, clopidogrel for the management of patients with non–ST-segment elevation acute coronary syndromes.

In summary, no potential sources of uncertainty (unrelated to research) were identified for EECP. For CLOP, the patent was expected to expire at a later point in time, and other information indicated that a new technology relevant to CLOP might be expected. Therefore, a "no" at point 5 is reached for EECP, whereas a "yes/no" conclusion is reached for CLOP. This reduces the potential pathways from 14 to 6 for EECP (assessments 17–26 in Table S1), whereas the number of potential pathways for CLOP remains unchanged (assessments 3–5 in Table S1) for the next point of assessment on the checklist.

Point 6—Are the Benefits of Research Greater than the Costs?

The sixth point on the checklist requires a judgment of whether the benefits of research are likely to exceed the costs. This requires an assessment of 1) the likelihood that research will be conducted, 2) when the results are likely to be available, 3) how much uncertainty is likely to be resolved, and 4) the likely impact of any other sources of uncertainty identified at point 5. The decision at this point can lead directly to guidance. However, if the benefits of research exceed the costs but research is not possible with approval, or if there are significant irrecoverable costs, guidance will depend on whether the benefits of approval are judged to exceed the costs (point 7 of the checklist).

Even if research is recommended in OIR or AWR, it might not be undertaken or completed. The potential gains from research depend on the likelihood of successful completion and the time taken to report the results. For example, if treatment decisions are irreversible in CLOP, it is only those patients incident after research is reported who will realize any of the potential benefits. If treatment decisions are reversible (chronic condition)—for example, in EECP—patients prevalent while the research is undertaken will not benefit immediately, but those who survive can benefit from the results. How long research might take to report will depend, in part, on the design, recruitment, size of population, and efficiency of data collection.

Most research will not inform all the parameters that determine the expected cost and QALYs. Therefore, the potential benefits of research will not be the total expected costs of uncertainty but instead some part of it. The potential value of research for CLOP over a range of times to report is illustrated in Figure 3 for all parameters and relative treatment effects. The potential value of research is likely to exceed the costs unless research takes more than 8 years to report. The patent for CLOP was due to expire 7 years after the appraisal. In this case, a significant fall in price in year 7 will substantially reduce the uncertainty surrounding 12 months of treatment with CLOP. If the new technology expected to enter the market at year 5 makes CLOP obsolete, there is no value in the evidence generated by research about CLOP. However, if the new technology has an NHE similar to that of CLOP and the uncertainty surrounding its expected cost-effectiveness is also similar, research about CLOP has more potential value in the future because it will also help

Table 3 – Population NHE over the technology time horizon for different policies.

CLOP	Approve	OIR	AWR*	Reject	Value of AWR†	Uncertainty resolved at launch‡	Value of evidence at launch§
Expressed in QALY							
$T < T^*$ ($T = 2$)	3,680,187	3,681,480	3,682,995	3,671,660	1515	3,684,181	2701
$T > T^*$ ($T = 7$)	3,680,187	3,675,487	3,680,362	3,671,660	175	3,684,181	3994
NHE expressed in £ million							
$T < T^*$ ($T = 2$)	73,604	73,630	73,660	73,433	30	73,684	54
$T > T^*$ ($T = 7$)	73,604	73,510	73,607	73,433	4	73,684	80
EECP	**Approve**	**OIR**	**AWR**	**Reject**	**Value of AWR**	**Uncertainty resolved at launch**	**Value of evidence at launch**
Expressed in QALY							
$T = 3$	1,391,001	1,397,192	1,393,578	1,389,596	–3614	1,400,288	3096
$T = 7$	1,391,001	1,393,608	1,392,030	1,389,596	–1578	1,400,288	6680
Expressed in £ million							
$T = 3$	27,820	27,944	27,872	27,792	–72	28,006	62
$T = 7$	27,820	27,872	27,841	27,792	–32	28,006	134

AWR, Approval with Research; CLOP, clopidogrel for the management of patients with non–ST-segment elevation acute coronary syndromes; EECP, enhanced external counterpulsation for chronic stable angina; NHE, net health effect; OIR, Only in Research; QALY, quality-adjusted life-year.

* Expected population NHE if AWR is a possibility.

† Difference between AWR and the next best feasible policy (OIR for $T < T^*$ and Approve for $T > T^*$ for CLOP; OIR for EECP).

‡ Maximum NHE for the resolution of all uncertainty immediately.

§ Difference between the maximum NHE for the resolution of all uncertainty immediately and the next best available policy.

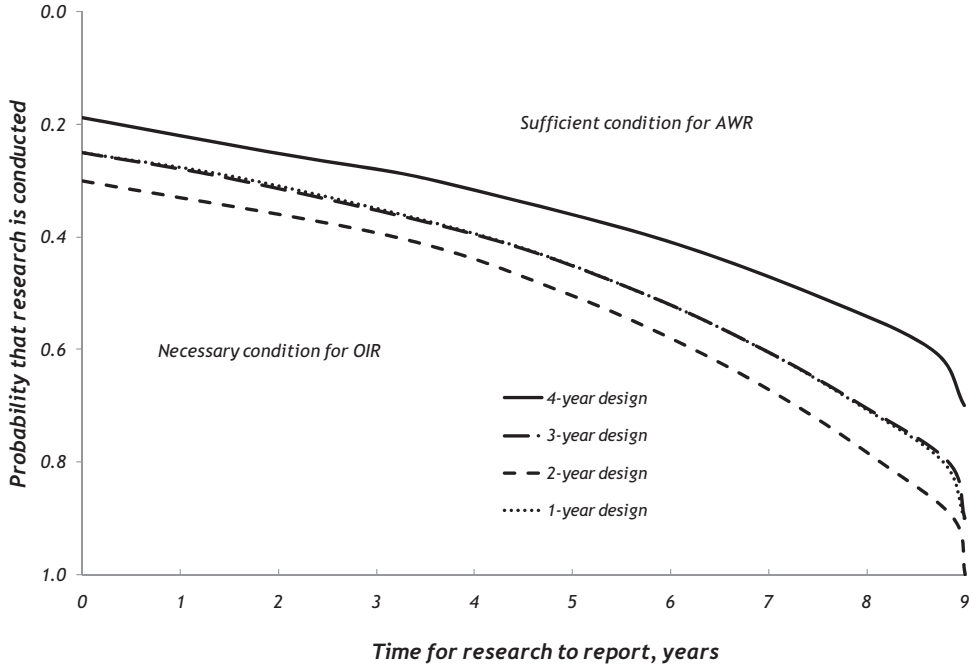

Fig. 4 – An OIR or AWR boundary (EECP). A boundary for when OIR rather than AWR might be appropriate for four research designs with different lengths of follow-up. For EECP, the type of research required is likely to report quickly for all research designs and with sufficient confidence that OIR would be appropriate even though the research could be conducted while EECP is approved. AWR, Approval with Research; EECP, enhanced external counterpulsation for chronic stable angina; OIR, Only in Research.

resolve some of the uncertainty in the choice between CLOP and the new technology for patients who become incident after that time.

In summary, the benefits of research are expected to be greater than the costs for EECP (although this will depend, in part, on research design) because the value of resolving the uncertainty at points 3 and 4 is very high relative to any expected costs of research. For CLOP, the potential value of research is likely to exceed the costs unless the research takes more than 8 years to report and assuming that the new technology has NHE similar to that of CLOP. Therefore, a "yes" at point 6 is reached for both EECP and CLOP, which reduces the potential pathways from 6 to 4 for EECP (assessments 17 and 18 and 24 and 25 in Table S1) and from 3 to 2 for CLOP (assessments 3 and 4 in Table S1) for the next point of assessment on the checklist.

Point 7—Are the Benefits of Approval Greater than the Costs?

The final point on the checklist requires a comparison of the benefits of approval and early access to current patients and the opportunity costs to future patients. The opportunity costs include the potential value of any research that may be forgone as a consequence and irrecoverable costs committed by approval. The decision at this point always leads directly to guidance.

Research that would provide more precise estimates of the relative treatment effect of CLOP and shorter treatment durations is potentially valuable, but it is unlikely to be possible if 12 months of treatment is already approved for widespread use. Therefore, AWR may not be possible, and so the benefits of early access with CLOP (Approval) must be compared with the potential value of OIR. The difference in NHE between Approve and OIR over a range of times when research might be reported (taking account of the expected change in price at year 7 and research costs of £10 million) indicates that OIR will be appropriate only if the research is reported within 3 years of appraisal ($T^* = 3$) because beyond this time the NHE forgone by withholding access to CLOP will exceed the potential gains to future patients. There is no guarantee, however, that the research recommended as part of OIR guidance will be conducted. Therefore, the probability that research will report at a particular time also needs to be considered. If research is certain to report but will take 4 years, or if there is only a 50% chance of reporting within 1 year, then OIR would not be appropriate and 12-month treatment of CLOP should be approved.

The assessments for CLOP are summarized in Table 3. The difference in NHE between AWR (if possible) and the next best feasible policy (OIR when $T < T^*$ and Approve when $T > T^*$) is £30 million and £4 million, respectively. The difference in NHE if all uncertainty was resolved prior to appraisal (at launch) and the next best available policy (OIR when $T < T^*$ and Approve when $T > T^*$) is £54 million and £80 million, respectively, and represents the value of having access to the evidence needed at launch. This can inform policies that might make better and more relevant evidence available.

Unlike CLOP, EECP has significant irrecoverable opportunity costs. As a consequence, even if research is possible with approval, it is not clear that AWR would be appropriate because OIR avoids the commitment of irrecoverable costs until research findings are available and a more informed decision can be made. In this case, OIR offers greater expected NHE than AWR as long as research reports before 9 years. A boundary for when OIR rather than AWR might be appropriate is illustrated in Figure 4 for four research designs with differing follow-up lengths.

For the same reasons as CLOP, however, the type of experimental research required may not be possible. Now approval (through Approve rather than AWR) not only commits the type of irrecoverable costs discussed above but it also means that the potential value of evidence to future patients must also be forgone. The assessments for EECP are also summarized in Table 3. The difference between OIR and Approve is greater than

that between OIR and AWR. As long as the cost of the research exceeds the difference between OIR and Approve, OIR would be appropriate. The NHE for AWR is negative, indicating that even if AWR was possible it would not be appropriate. Like CLOP, having the evidence needed before appraisal is of value to the NHS, dependent on how long it would otherwise have taken for an OIR recommendation to deliver the same evidence; for example, £62 million if 3 years or £134 million if 7 years. The decision at this point always leads directly to guidance.

In summary, guidance for EECP will depend on whether technology can be approved for widespread use while research is conducted (i.e., yes/no at point 4 determines whether AWR is a possibility). The analysis at this final point, however, demonstrates that even when research is possible with approval, OIR appears to offer the greater expected NHE than does AWR or Approve as long as research reports before 9 years. This is largely because the consequences of committing significant irrecoverable costs through AWR or Approve are greater than the NHE forgone by restricting access to EECP through OIR. For CLOP, research was not considered possible with approval, and so the benefits of early access to 12 months of treatment with CLOP (Approval) must be compared with the potential value of OIR. The analysis at this final point indicates that if research reports earlier than 3 years, OIR would be appropriate; otherwise, Approve would be more appropriate.

Discussion

Decision options of OIR and AWR have emerged in many health care systems to balance the need for early access to a technology and the need for valuable research to be conducted. In the United States, the term "coverage with evidence development" is often used as a catch-all term for OIR/AWR-type schemes. The Centers for Medicare and Medicaid Services issue both OIR- and AWR-type coverage decisions under two distinct processes of coverage with appropriate determination and coverage with study participation [21]. In the United Kingdom, an OIR scheme can be recommended by NICE when appraising technologies. Following an OIR recommendation, however, there are no formal arrangements to develop the research study required to reduce uncertainties [22]. NICE does not hold a budget to commission research, and, therefore, much of the burden falls on the manufacturer.

Several previous attempts have been made to develop taxonomies for conditional coverage and risk-sharing schemes [23–27]. However, these have not specifically focused on OIR/AWR schemes. For example, in the taxonomy developed by Carlson et al [23], conditional coverage schemes are divided into coverage with evidence development and conditional treatment continuation schemes. Within coverage with evidence development, two subtypes are presented: OIR and "Only with Research," wherein Only with Research is similar to AWR.

Claxton et al [10] set out to develop a set of principles and criteria that may be required to reach OIR/AWR-type decisions. The result was a sequence of assessments and judgments, summarized as a seven-point checklist. This article has illustrated the use of the checklist to two case studies.

The analysis shows how the checklist might be operationalized, what types of analyses might feasibly be included within an appraisal process, and how the results might be interpreted to inform the judgments required. We also show how the different types of guidance (Approve, AWR, OIR, or Reject) might be reached in different ways. The order of considerations means that all seven assessments do not necessarily need to be made when an earlier judgment can lead directly to guidance. The assessment of whether further research might be worthwhile and what type of evidence might be required would need to be undertaken routinely under such a framework. If research may be worthwhile, some indication of the type of evidence needed would also be useful for those making an assessment of the prospects of research and whether the type of research required to generate it would be possible with approval. Therefore, routine assessment up to point 4 of the checklist would seem appropriate before others with expertise in and responsibility for research design and commissioning consider the prospects of conducting research.

A limitation of this analysis is a lack of consideration of the diffusion of technologies. The potential health benefits of conducting further research are realized (i.e, patient outcomes actually improve) only if the findings of the research have an impact on clinical practice. There may be other mechanisms (e.g., more effective dissemination of existing evidence) or policies that fall within the remit of other bodies to influence the implementation and diffusion of technologies rather than acquiring additional evidence [28].

These case studies have demonstrated the feasibility of applying the checklist without requiring any substantial reanalysis of the original assessments. The information required to assess whether other sources of uncertainty will resolve over time (point 5 on the checklist), however, requires information that is not commonly reported during an appraisal process. It is also recognized that some amendments might be required when cost-effectiveness is not the prime consideration. Furthermore, the application of the checklist alone is unlikely to be sufficient because no quantitative analysis can capture all aspects of scientific and social value judgments. Therefore, the most relevant question is whether these methods offer a practical and useful starting point for deliberation and add to the transparency and accountability of adoption decisions.

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Supplemental Materials

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